Remarks

The Amendments

Claim 7 has been amended to depend from claim 2, which provides antecedent basis for the recitation in claim 7 of the pharmaceutically acceptable excipient.

The amendment adds no new matter and does not require a new search.

The Rejection of Claims 1-8 Under 35 U.S.C. § 112, first paragraph

Claims 1-8 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicant respectfully traverses the rejection.

The purpose of the written description requirement of 35 U.S.C. § 112, first paragraph is to ensure that the specification conveys to those skilled in the art that an applicant possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). What is required to satisfy the written description requirement depends on the nature of the invention claimed. *In re DiLeone*, 436 F.2d 1404, 1405, 168 U.S.P.Q. (BNA) 592, 593 (C.C.P.A. 1971).

Independent claims 1 and 8 each recite an encapsulating material "which is selected to be dissolution resistant at a pH of about 4 or 5 or less and to readily dissolve at a pH of greater than about 4 to 5." The Office Action asserts that the functional description of the recited material "will not substitute for the written description of the structure of the compound." All that is required to satisfy the written description requirement, however, is that the specification convey to those skilled in the art that Applicant possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117

(Fed. Cir. 1991). *See also Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1327, 63 U.S.P.Q.2d (BNA) 1609, 1615 (Fed. Cir. July 15, 2002): "the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed." The present specification satisfies this requirement.

The claimed subject matter includes orally deliverable pharmaceutical compositions comprising 2'-deoxy-2'-(fluoromethylene)cytidine and methods of enhancing oral bioavailability of compositions of 2'-deoxy-2'-(fluoromethylene)cytidine. The specification teaches that, in spite of the teachings in the art that oral administration of 2'-deoxy-2'-(fluoromethylene)cytidine ("FMdC") is the preferred route of delivery, oral delivery of previous formulations did not provide for acceptable bioavailability of the drug and that merely protecting FMdC from acidic degradation is insufficient to provide maximum bioavailability. Page 3, lines 3-4 and 18-19. Instead, Applicant has discovered that what is required is an encapsulation material that is dissolution resistant at pH 4 to 5 or less but readily dissolves at a pH greater than 4 to 5. Page 4, lines 21-23.

Based on this discovery, claims 1-8 recite the genus of such encapsulation materials. The U.S. Patent and Trademark Office's Written Description Guidelines set forth means by which the written description requirement for a recited genus may be satisfied:

> 2) For each claim drawn to a genus:
>
> > The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

66 Fed. Reg. 1099, 1106 (January 5, 2001), internal references omitted. The Guidelines also state that "[s]atisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." *Id.*

The specification provides examples of species of the recited genus at page 10, lines 21-26:

> Preferred materials for the enteric coating include, by way of example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, poly(vinyl acetate phthalate), hydroxypropyl methylcellulose acetate succinates, cellulose acetate phthalate/diethylphthalate, and, preferably, poly(meth)acrylates. The latter include copolymers of methacrylic acid and acrylic acid esters and/or methacrylic acid esters.

These species of enteric coatings were known in the art before the present specification was filed and were known to possess common attributes or features. See, for example, U.S. Patent 6,139,875, issued October 31, 2000 and filed September 29, 1998:

> Polymers useful as enteric coatings contain ionizable carboxylic groups and include cellulose acetate phthalates(C-A-P), cellulose acetate trimellitates(C-A-T), hydroxypropyl methyl cellulose phthalates(HPMCP), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), polyvinyl acetate phthalate (PVAP), and certain acrylic polymers. In the low pH stomach environment, the carboxylic acid groups in the polymers remain un-ionized. Therefore, the polymeric coating remains insoluble in gastric fluid. The polymeric coating disintegrates or dissolves in the higher pH intestinal environment to allow dissolution of the tablet core in the small intestine. The active ingredients are absorbed through the intestinal wall for delivery to the blood stream.

Col. 1, lines 26-32. Such polymers "containing carboxyl groups which remain insoluble at a pH below about 4 (gastric pH range), but which ionize, and thus cause the polymer to dissolve, at a

pH above about 5.0 (intestinal pH range)." Col. 3, lines 23-27. Thus, there is a known correlation between the structure of the disclosed species and their ability to "be dissolution resistant at a pH of about 4 to 5 or less and to readily dissolve at a pH of greater than about 4 to 5," as recited in claims 1-8.

Provided with the disclosure in the specification of a representative species of the recited genus of enteric coating materials, together with the known correlation between the structure of such materials and their function, one of skill in the art would have recognized that Applicant was in possession of the recited genus of enteric coating materials. Thus, the written description requirement is satisfied.

Applicant respectfully requests withdrawal of the rejection.

The Rejection of Claim 7 Under 35 U.S.C. § 112, second paragraph

Claim 7 stands rejection under 35 U.S.C. § second paragraph as indefinite. Applicant respectfully traverses the rejection.

Applicant thanks the Examiner for pointing out that claim 7 should properly depend from claim 2. The correction has been made. Applicant respectfully requests withdrawal of the rejection.

The Rejection of Claims 1-5, 7, and 8 Under 35 U.S.C. § 103(a)

Claims 1-5, 7, and 8 stand rejected under 35 U.S.C. § 103(a) as obvious over McCarthy *et al.*, U.S. Patent 5,378,693 ("McCarthy") in view of Huber *et al.*, U.S. Patent 4,180,559 ("Huber"). Applicant respectfully traverses the rejection.

Claims 1-5 and 7 each recite an orally deliverable pharmaceutical composition

comprising 2′-deoxy-2′-(fluoromethylene)cytidine which is encapsulated in a material which is selected to be dissolution resistant at a pH or about 4 to 5 or less and to readily dissolve at a pH of greater than about 4 to 5. Claim 8 recites a method of enhancing oral bioavailability of 2′-deoxy-2′-(fluoromethylene)cytidine that includes the step of encapsulating 2′-deoxy-2′-(fluoromethylene)cytidine in such a material. The U.S. Patent and Trademark Office must make three showings to establish a *prima facie* case that claims 1-5, 7, and 8 are obvious:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142. A *prima facie* case of obviousness has not been made based on the cited combination because the ordinary artisan would have had no motivation to combine the teachings of McCarthy and Huber.

McCarthy is cited as disclosing formulations of 2′-deoxy-2′-(fluoromethylene)cytidine (FMdC) with various excipients, as well as the oral administration of such formulations. Huber is cited as disclosing hydroxypropyl methylcellulose phthalate as an enteric coating. The Office Action asserts it would have been obvious for one of ordinary skill in the art to have used the hydroxypropyl methylcellulose phthalate of Huber in combination with the FMdC of McCarthy. The motivation for making the combination is said to be that the concept of using enteric coatings to protect drugs from gastric fluids was well known and that both McCarthy's shellac and Huber's hydroxypropyl methylcellulose phthalate "meet most of the criteria of a good enteric coating and they are among the most widely used coating materials for this purpose."

Page 6, second full paragraph. That is, the rejection is based on the view that the two coatings are equivalent. This view, however, is incorrect.

As noted in the Office Action, McCarthy teaches that coatings such as sugar, shellac, or other enteric coating agents are suitable for oral formulations of 2'-deoxy-2'-(fluoromethylene)cytidine. Col. 25, lines 40-41. But the present specification explicitly teaches that the coatings disclosed in McCarthy – including shellac – would not be suitable for the orally deliverable pharmaceutical compositions recited in claims 1-5, 7, and 8:

> merely protecting FMdC from acidic degradation is insufficient in obtaining maximal bioavailability for this drug. Specifically, bioabsorption initiates in the upper portions of the small intestine where the pH can be as low as about 4 to 5. Encapsulation of FMdC in materials which are resistant to acidic pH would result in undesirable loss of bioabsorption in this portion of the gastrointestinal tract.
>
> Thus, for example, ***tablets or pills coated with sugar or shellac as coating agents, as disclosed in U.S. Patent 5,378,693 [McCarthy], would not be desirable.***

Page 3, lines 18-25, emphasis added. There is no indication at all in McCarthy that sugar or shellac would not be suitable for obtaining maximum bioavailability of FMdC. Hydroxypropyl methylcellulose phthalate, on the other hand, has specific properties not possessed by sugar or shellac, and these properties were known to the ordinary artisan when the present specification was filed. See Huber, at col. 2, lines 36-42:

> The coatings described herein are of such a nature as to protect the compound 1-(2-chlorodibenzo[b,f]oxepin-10-yl)-4-methylpiperazine from acid degradation in strongly acidic gastric fluids, but are designed to dissolve at the weakly acidic pH of 5.0 to 5.5 in order to permit dissolution and absorption of the drug substance.

A *prima facie* case of obviousness requires a showing that the cited references themselves or the knowledge generally available to one of ordinary skill in the art contain a

suggestion or motivation to combine the reference teachings. M.P.E.P. § 2142. Motivation to combine references can come from three possible sources: "the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d (BNA) 1453, 1457-58 (Fed. Cir. 1998). None of these three possible sources provides sufficient motivation for the ordinary artisan to have combined the cited references.

The nature of the problem to be solved is how to maximize the bioavailability of orally administered 2′-deoxy-2′-(fluoromethylene)cytidine, particularly for the treatment of neoplastic or viral disease. The prior art (*e.g.*, McCarthy) teaches that FMdC can be used to slow, interrupt, arrest, or stop growth or metastasis of a carcinoma (col. 23, lines 53-55) and that oral administration is preferred for this purpose (col. 24, line 21). The prior art also teaches that enteric coatings such as sugar and shellac (*i.e.*, coatings that merely resist acidic pH) are suitable for making formulations of 2′-deoxy-2′-(fluoromethylene)cytidine for oral delivery. Col. 25, lines 40-41. McCarthy contains absolutely no teaching or suggestion that such formulations would not provide sufficient bioavailability for the disclosed purpose of treating a carcinoma or that enteric coatings with the properties of hydroxypropyl methylcellulose phthalate are either desirable or should be used to make orally deliverable pharmaceutical compositions of 2′-deoxy-2′-(fluoromethylene)cytidine. On the other hand, Huber contains no teaching or suggestion that hydroxypropyl methylcellulose phthalate or other enteric coatings with similar properties should be used to encapsulate 2′-deoxy-2′-(fluoromethylene)cytidine.

Finally, absent the teachings of the present specification, the ordinary artisan would not have known that enteric coatings with the recited property of being dissolution resistant at a pH

or about 4 to 5 or less and to readily dissolve at a pH of greater than about 4 to 5 should be used to maximize bioavailability of 2'-deoxy-2'-(fluoromethylene)cytidine. In fact, the U.S. Patent and Trademark Office has used Applicant's teachings as a template to select these elements of the cited references. Hindsight use of Applicant's specification, however, is not permitted.

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

In re Rouffet, 47 U.S.P.Q.2d (BNA) 1453, 1457-58 (Fed. Cir. 1998).

The U.S. Patent and Trademark Office has not shown a motivation sufficient for the ordinary artisan to have combined the teachings of McCarthy and Huber. Thus, a *prima facie* case of obviousness of claims 1-5, 7, and 8 has not been made. Applicant respectfully requests withdrawal of the rejection.

The Rejection of Claims 1-8 Under 35 U.S.C. § 103(a)

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) as obvious over McCarthy in view of Huber and further in view of Ohno *et al.*, U.S. Patent 4,017,647 ("Ohno"). Applicant respectfully traverses the rejection.

This rejection adds Ohno to the combination of references discussed above. Ohno is cited as teaching methods of producing enteric coatings that are soluble at pHs ranging from 4 to 8. In particular, Ohno is cited as disclosing copolymers of methacrylic acid and acrylic acid esters and copolymers of methacrylic acid and methacrylic acid esters, as recited in claim 7. The Office Action asserts it would have been *prima facie* obvious to have used such enteric coatings in place of those disclosed in McCarthy because these coatings permit compounds to be dissolved in the intestine.

This rejection is defective for the same reasons as the rejection of claims 1-5, 7, and 8 over McCarthy in view of Huber: the ordinary artisan would have had no motivation to have used the coatings such as those disclosed in either Huber or Ohno with McCarthy's FMdC. Again, the rejection views the enteric coatings of Huber and Ohno as equivalent to those disclosed in McCarthy, which is incorrect. McCarthy does not teach or suggest that coatings with the particular properties of those taught in Huber and Ohno are either desirable or required to for bioavailability of orally administered FMdC. It is only the present specification that teaches use of such coatings to maximize bioavailability of orally administered FMdC. Hindsight use of the present specification is not permitted. *In re Rouffet*, 47 U.S.P.Q.2d (BNA) at 1457-58.

A *prima facie* case of obviousness has not been made. Applicant respectfully requests withdrawal of the rejection.

Please continue to address all correspondence to Dr. Steven Collier, Chiron Corporation, Reg. No. 42,429, Chiron Corporation, Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2917 (telephone 510-923-2718; FAX 510-655-3542).

Respectfully submitted,

Date: December 31, 2002

By: Lisa M. Hemmendinger
Lisa M. Hemmendinger
Registration No. 42,653

Banner & Witcoff, Ltd.
1001 G Street, N.W., Eleventh Floor
Washington, D.C. 20001-4597
(202) 508-9100

Appendix 1. Version of Amended Claims with Markings to Show Changes Made

7. (amended) The orally deliverable pharmaceutical composition according to Claim [1] 2 wherein the composition comprises from about 50 to about 99.5 weight percent of the pharmaceutically acceptable excipient(s) and from about 0.5 to about 50 weight percent of 2'-deoxy-2'-(fluoromethylene)cytidine.